# WHERE DOES THE PENTOTHAL GO?

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THIOPENTAL is a weak acid, existing largely as undissociated molecules in the physiological range of pH. It is these un-ionized molecules which are pharmacologically active. Being highly lipid-soluble, they pass readily through lipoid membranes such as the blood/brain and other blood/tissue barriers. Less lipid-soluble barbiturates, which penetrate the brain more slowly, are less suitable as anesthetics. For example, dogs do not fall asleep until 30 to 40 minutes after therapeutic doses of barbital intravenously, or 20 to 30 minutes after phenobarbital, these being the times required for passage across the blood/brain barrier.[1] This is explained by the low lipid solubility of these drugs, as shown in Table I. Indeed, thiopental is so highly lipid-soluble that its onset of action is limited primarily by the circulation time to the brain. For the same reason the passage of thiopental into other tissues of the three body compartments (vital organs, lean body mass, depot fats) is largely but by no means exclusively a function of the blood flow to each.

Let us now consider the events comprising the sojourn of a single dose of thiopental in the body from the moment of administration, when all of the drug is within the blood stream and the plasma concentration is at its maximum, to the ultimate time many hours later when the plasma concentration is zero as the last vestige of drug has been metabolized. Brodie and Hogben[2] have depicted these events in the scheme shown in Figure 1, in which the closed rectangle represents the plasma volume. Although the factor of absorption must be reckoned with in using thiopental rectally[3] or intramuscularly,[4] it can be ignored in the present discussion on the assumption that the drug has been administered intravenously.

About 25 per cent of the thiopental present in plasma during anes-

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TABLE I.—RELATIVE OIL TO WATER PARTITION RATIOS[1]

| | | | |
|---|---|---|---|
| Barbital | 0.26 | Thiobarbital | 2.3 |
| Phenobarbital | 1.0 | Thiophenobarbital | 11 |
| Pentobarbital | 5.8 | Thiopental | 63 |

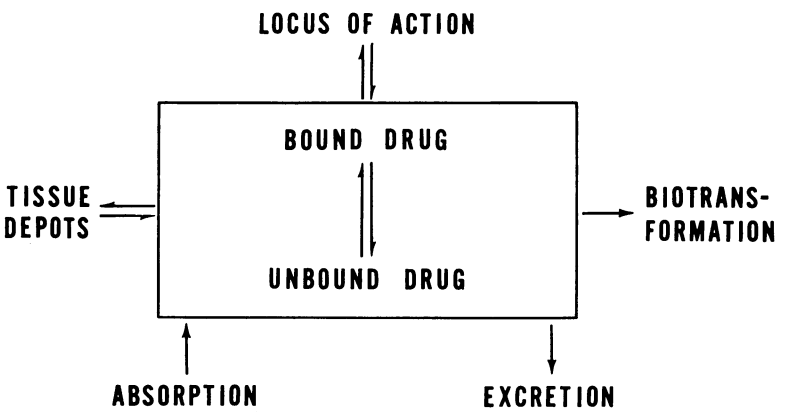


Fig. 1. Drug uptake, distribution and fate in the body.[2]

thesia is free in plasma water. This represents the fraction of drug available for pharmacological action. The remaining 75 per cent of the thiopental is bound to protein, presumably plasma albumin.[5] This is an unstable type of bonding, readily reversible with changes in concentration. It may be considered as a means of thiopental transport in the blood stream, somewhat analogous to oxygen transport by hemoglobin, except that oxyhemoglobin is a chemical compound while albumin and thiopental form a loose structural complex held together by forces of physical attraction acting at their surfaces.[6] At very low concentrations many hours later, binding increases to 88 per cent.[7] The clinical significance of this finding is not yet known.

From the moment of intravascular administration thiopental begins to pass into its locus of action (i.e., into the brain) and into pharmacologically inert tissue depots in the three body compartments. These events occur simultaneously but at different rates, depending primarily upon the circulation to the component structures within each compartment. Maximal concentrations appear in the brain prac-

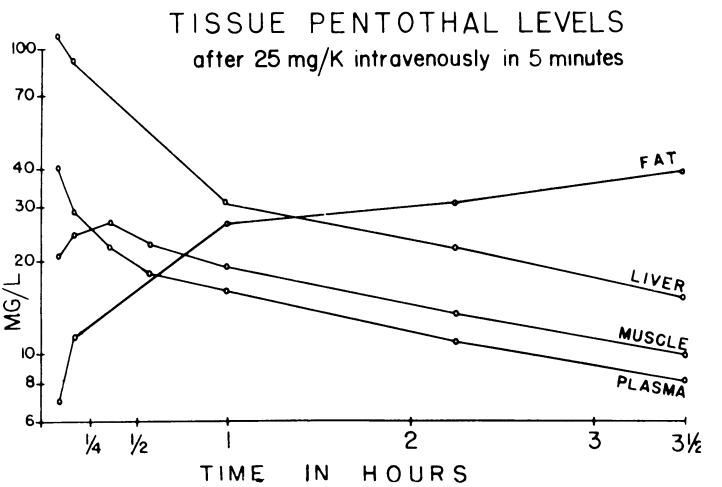


Fig. 2. Concentrations of thiopental in dog tissues at various times from the beginning of the injection.[11]

tically instantaneously (i.e. within one to two circulation times), with prompt onset of sleep.[8] Yet perfusion of the brain, although rich, is far from uniform, as demonstrated autoradiographically in animals by Landau *et al.*[9] using as the indicator substance trifluoriodomethane-$I^{131}$. In the conscious state, the highest rates of blood flow were found in the visual, auditory and somatosensory areas of the cerebral cortex, the geniculate bodies and the inferior colliculus. Correspondingly, Roth and Barlow[10] observed high radiodensity (indicating high concentrations of drug) in the same areas examined similarly one minute after the intravenous injection of thiopental-$C^{14}$; at 30 minutes distribution was uniform. It is interesting to note that, during light thiopental anesthesia, significant reductions in blood flow were observed in all of the above-named structures, especially in the primary sensory areas of the cortex.[9]

Other organ tissues comprising the remainder of the richly perfused visceral compartment also receive thiopental rapidly. Thus, maximal drug concentrations were observed in liver immediately following administration.[11] Although similar measurements have not been attempted with other vital organs, analogous findings may be presumed. In short, the thiopental in the blood stream initially floods into vital organs, including the brain, thereby causing the patient to fall asleep.

TABLE II.—PASSAGE OF THIOPENTAL INTO FAT[14]

| *Subject, male* | *Dose* | *Time after dose* | *Omental fat mg./kg.* | *Subcutaneous fat, mg./kg.* |
|---|---|---|---|---|
| 157 lb., medium | 500 mg. IV in 5 min. | 1 hr. 36 min. | 36.8 | 18.6 |
| | | 2 hr. 19 min. | 33.6 | 20.3 |
| 142 lb., av. medium | 2.3 gm. IV in 36 min. | 29 min. | 122 | 62 |
| | | 1 hr. 45 min. | 140 | 87.5 |
| | | 2 hr. 4 min. | 135 | 87 |

Awakening requires the departure of sufficient drug from the brain so that the residual concentration is inadequate to maintain a hypnotic effect. Consequently, the question "Where does the Pentothal go?" will be answered by finding where in the body levels of thiopental continue to rise beyond the initial moments when uptake by brain has ceased.

Concurrently from the beginning thiopental is being distributed into the poorly perfused tissue components of the lean body mass (i.e., muscle, skin, connective tissue, bone, etc.) and of the depot fats (Figure 2). Drug concentrations in canine muscle, although high at first, continue to rise for a short period, reaching a peak about 15 to 20 minutes after the end of injection. Since muscle mass alone represents 43 per cent of the animal's total body weight,[12] this seemingly small rise actually represents about 46 per cent of the thiopental administered. Price and co-workers[13] noted similar findings in man: maximal concentrations of drug occurred at 30 minutes in samples of rectus muscle obtained from two human subjects during herniorrhaphy. In other words, up to no more than 30 minutes following injection, the answer to the question: "Where does the Pentothal go?" may be, in large part, "Into lean body mass"; beyond 30 minutes at most, levels here too are falling and yet another answer must be sought.

Meanwhile, however, thiopental is also entering fat depots throughout the body. Table II presents data obtained from serial biopsies of omental and subcutaneous fat in man.[14] The consistently higher values for thiopental concentrations in omental fat are doubtless attributable to the relatively greater blood flow through the arterial arcades in the omentum as compared with the more poorly perfused subcutaneous layer of adipose tissue. Table III presents the same data recalculated to

TABLE III.—THIOPENTAL IN FAT

| *Dose* | *Time after dose* | *Amount of drug in fat* | |
|---|---|---|---|
| | | *mg.* | *% dose* |
| 500 mg. IV | 1 hr. 36 min. | 251 | 49 |
| in 5 min. | 2 hr. 19 min. | 271 | 53 |
| 2.3 gm. IV | 29 min. | 827 | 36 |
| in 36 min. | 1 hr. 25 min. | 1167 | 51 |
| | 2 hr. 4 min. | 1160 | 51 |

show the content of thiopental in fat expressed as a percentage of the original dose. To this end, the lower values found in subcutaneous fat were taken to represent the average concentration in all fat depots, while the individuals concerned, both of medium build, were considered equivalent to the "average" man found by Soberman [15] and others to contain 20 per cent fat. The results show that by 1½ hours after the end of administration 50 per cent of the drug injected has found its way into fat and that 36 per cent has done so within 30 minutes. Somewhat similar findings in man were reported by Shideman [16] and his colleagues, whose data showed maximum localization in human subcutaneous fat within 30 to 75 minutes. Such early and extensive localization of thiopental in fat must be ascribed primarily to the high lipid solubility of the drug, since the rate of blood flow is essentially the same to both fat and resting muscle.[17] In time, thiopental concentrations in each fat depot become the same (i.e., in this respect the depots are in equilibrium with each other and with the rest of the body), finally starting to fall at about five hours.[7] The lateness of equilibration has been erroneously interpreted to signify that thiopental uptake by fat is relatively unimportant until much later, more than 8 hours after injection.[13] This conclusion was based upon a computer solution, which seems to have indicated a slow and a relatively uniform rate of uptake by fat. Actually, the rate of thiopental accumulation in fat is maximal early enough (within the first 1½ hours or so) to contribute significantly to clinical recovery following the use of this agent, and becomes slower only later on as equilibrium is approached. Intercompartmental diffusion on a large scale, as described by Perl,[18] could doubtless contribute to a transfer of the highly lipid-soluble thiopental into fat from

adjacent tissues directly rather than via the circulation; but this effect remains to be demonstrated.

The above findings may be restated as follows: within the first 30 minutes, the answer to the question, "Where does the Pentothal go?" is: "Into both lean body mass and fat depots," with lean mass more important because of its greater bulk. From 30 minutes to about 1½ hours, the answer is: "Into fat alone," since this is the only tissue which continues to acquire thiopental. Beyond 1½ hours, additional uptake even by fat is of minor import. With nowhere else for the drug to go, eventual awakening depends upon removal of thiopental from the body by excretion or destruction or both.

Actually since less than 0.3 per cent is excreted unchanged in the urine,[5] biotransformation by enzyme systems residing in liver microsomes ultimately disposes of the administered thiopental. A major route of metabolism in man is side chain oxidation to form thiopental carboxylic acid.[5] Desulfuration to form pentobarbital has also been demonstrated in man;[19] because pentobarbital is an active barbiturate, this form of biotransformation is not an aid to "detoxification." In any event, the rate of disappearance of thiopental from human plasma, after distribution into tissues has been virtually completed, is no greater than 9 to 15 per cent per hour.[20] The microsomal enzymes might well be capable of metabolizing thiopental more rapidly than these figures would indicate. The rate-limiting factor may be slow release from fat depots, maintaining plasma concentrations at low levels for considerable periods of time. This could account in part for prolonged somnolence during recovery from large doses of thiopental.

## Summary

Administered thiopental swiftly enters the brain (and other richly-perfused vital organs), with prompt onset of sleep. Following a small dose, awakening is also prompt, as concentrations in brain and plasma fall rapidly below anesthetic levels because of the continuing distribution of drug to other tissues of the lean body mass and fat depots. In this early awakening (within 30 minutes) lean mass is more important than fat because of its greater bulk; but fat does participate. After larger dosage, awakening is delayed beyond 30 minutes, with thiopental now leaving both viscera and lean tissues but up to about 1½ hours continuing to enter fat at a considerable rate; metabolism to a minor

extent is also occurring. After still larger dosage, awakening is of course greatly delayed; beyond 1½ hours fat continues to accumulate thiopental too slowly to be helpful. The further disappearance of thiopental from the body now depends solely upon the slow process of drug metabolism, and postanesthetic depression is apt to be greatly prolonged.

## *REFERENCES*


1. Mark, L. C. and others. Passage of thiobarbiturates and their oxygen analogs into brain, *J. Pharmacol. Exp. Ther. 123*:70-73, 1958.
2. Brodie, B. B. and Hogben, C. A. M. Some physico-chemical factors in drug action, *J. Pharm. Pharmacol. 9*:345-80, 1957.
3. Mark, L. C., Fox, J. L. and Burstein, C. L. Preanesthetic hypnosis with rectal Pentothal in children, *Anesthesiology 10*:401-05, 1949.
4. Dhruva, A. J. Intramuscular use of Pentothal sodium as an aid to pediatric anesthesia, *Anesth. Analg. (Cleveland) 39*:237-39, 1960.
5. Brodie, B. B. and others. Fate of thiopental in man and a method for its estimation in biological material, *J. Pharmacol. Exp. Ther. 98*:85-96, 1950.
6. Mark, L. C. Factors modulating barbiturate action, *Far East J. Anesth. 4*: (2) 1, 1963.
7. Brand, L. and others. Further studies of the uptake of thiopental by human fat, *Fed. Proc. 22*:479, 1963.
8. Mark, L. C. and others. Passage of thiopental into brain, *J. Pharmacol. Exp. Therap. 119*:35-38, 1957.
9. Landau, W. M. and others. Local circulation of the living brain; values in the unanesthetized and anesthetized cat, *Trans. Amer. Neurol. Ass. 80*:125-29, 1955.
10. Roth, L. J. and Barlow, C. F. Drugs in the brain, *Science 134*:22-31, 1961.
11. Brodie, B. B., Bernstein, E. and Mark, L. C. Role of body fat in limiting the duration of action of thiopental, *J. Pharmacol. Exp. Therap. 105*:421-26, 1952.
12. Skelton, H. Storage of water by various tissues of the body, *Arch. Intern. Med. 40*:140-52, 1927 (quoted by Bard, P. In *Medical Physiology*. St. Louis, C. V. Mosby, 1956, p. 744).
13. Price, H. L. and others. Uptake of thiopental by body tissues and its relation to the duration of narcosis, *Clin. Pharmacol. Ther. 1*:16-22, 1960.
14. Mark, L. C. Thiobarbiturates. In *Uptake and Distribution of Anesthetic Agents*, E. M. Papper and R. J. Kitz, eds.. New York, McGraw-Hill Book Co., 1963.
15. Soberman, R. and others. Use of antipyrine in the measurement of total body water in man, *J. Biol. Chem. 179*:31-42, 1949.
16. Shideman, F. E. and others. Distribution and in vivo rate of metabolism of thiopental, *J. Pharmacol. Exp. Therap. 107*:368-78, 1953.
17. Perl, W. Lesser, G. T. and Steele, J. M. Kinetics of distribution of the fat-soluble inert gas cyclopropane in the body, *Biophys. J. 1*:111-35, 1960.
18. Perl, W. Large-scale diffusion between body compartments. In *Uptake and Distribution of Anesthetic Agents*, E. M. Papper and R. J. Kitz, eds., New York, McGraw-Hill Book Co., 1963.
19. Soehring, K. and Dietz, W. Pentobarbital—ein Abbauprodukt von Thiopental. *Klin. Wschr. 34*:705-06, 1956.
20. Mark, L. C. Metabolism of barbiturates in man, *Clin. Pharmacol. Ther. 4*:504-30, 1963.